Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study

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Previous studies of recipients of hematopoietic stem-cell transplants suggest that graft-versus-host disease (GVHD) and its therapy may increase the risk for solid cancers, particularly squamous-cell carcinomas (SCCs) of the buccal cavity and skin. However, the importance and magnitude of these associations are not well characterized. We conducted a case–control study of 183 patients with post-transplantation solid cancers (58 SCCs, 125 non-SCCs) and 501 matched control patients within a cohort of 24 011 patients who underwent hematopoietic stem-cell transplantation (HSCT) at 215 centers worldwide. Our results showed that chronic GVHD and its therapy were strongly related to the risk for SCC, whereas no increase in risk was found for non-SCCs. Major risk factors for the development of SCC were long duration of chronic GVHD therapy (*P* < .001); use of azathioprine, particularly when combined with cyclosporine and steroids (*P* < .001); and severe chronic GVHD (*P* = .004). Given that most patients who received prolonged immunosuppressive therapy and those with severe chronic GVHD were also treated with azathioprine, the independent effects of these factors could not be evaluated. Additional analyses determined that prolonged immunosuppressive therapy and azathioprine use were also significant risk factors for SCC of the skin and of the oral mucosa. These data provide further encouragement for strategies to prevent chronic GVHD and for the development of more effective and less carcinogenic treatment regimens for patients with moderate or severe chronic GVHD. Our results also suggest that clinical screening for SCC is appropriate among patients exposed to persistent chronic GVHD, prolonged immunosuppressive therapy, or both. (Blood. 2005; 105:3802-3811)

Introduction

Allogeneic transplantation of hematopoietic stem cells from bone marrow, peripheral blood, or cord blood offers curative therapy for malignant and nonmalignant lymphohematopoietic diseases and other disorders. The success rate has improved progressively, and some surviving patients have now been followed up for more than 3 decades.[1] One important complication among transplantation survivors is the development of new (secondary) malignancies, particularly solid tumors[2-10] and posttransplantation lymphoproliferative disorders.[3,8,11,12] Previous studies report that transplant recipients who develop chronic graft-versus-host disease (GVHD) are at especially high risk for squamous-cell carcinoma (SCC) of the oral cavity and skin,[6,7,9,10,13,14] with more aggressive behavior noted for some of these tumors.[15] However, the relative importance of this association between chronic GVHD and type and duration of immunosuppressive therapy used for GVHD has never been systematically examined in a large cohort. Among recipients of solid organ transplants, the frequency of rejection episodes (requiring intensified immunosuppression) and the duration of immunosuppressive

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therapy are strongly related to the occurrence of skin cancer.[16] Patients undergoing hematopoietic stem-cell transplantation (HSCT), in contrast to those undergoing solid organ transplantation, generally receive immunosuppressive therapy for limited periods of time unless they develop chronic GVHD. Thus, prolonged immunosuppression and chronic GVHD are usually linked. Here, we report the results of a case–control analysis in recipients of hematopoietic stem-cell transplants designed to quantify the association between GVHD and its therapy and the development of secondary SCC.

Patients, materials, and methods

Patients

A case–control study was conducted in a cohort of 24 011 patients who underwent allogeneic or syngeneic HSCT reported to the Center for International Blood and Marrow Transplant Research (CIBMTR; n = 18 488; transplantations from 1964 through 1994, followed up through 1995) or at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle (n = 5523; transplantations from 1969 through 1996, followed up through 1997). The range in follow-up was less than 0.1 to 26.4 years; mean follow-up was 6.0 years among the 9966 patients alive at study end. Bone marrow was the source of stem cells in more than 95% of the procedures during the study period; consequently, patients receiving peripheral blood or cord blood grafts were excluded from the analysis. All patients underwent myeloablative preparative regimens. Centers reporting to the CIBMTR were selected for participation on the basis of completeness of patient follow-up and willingness to collect supplemental detailed pretransplantation and posttransplantation data. Second cancers were identified in a prospective manner through the Long-term Follow-up Program at FHCRC (including biannual or annual questionnaires) and by routine follow-up reports submitted annually to the CIBMTR. Reports of second cancers were reviewed and, if necessary, reclassified (William D. Travis) according to available pathology and physician records.

We identified 183 patients in whom invasive (n = 171) or in situ (n = 12) solid cancers developed. Invasive SCCs of the skin and melanomas of the skin were included, but in situ nonmelanoma skin cancers and basal cell skin cancers were excluded. For each patient with a solid tumor (case patient), we randomly selected control patients from the total cohort. We attempted to match at least 3 controls per case patient using the following criteria: registry (CIBMTR, FHCRC), type of donor (allogeneic, syngeneic), primary disease, sex, age at transplantation (within 3 years), and survival time at least as long as the interval from transplantation to post-HSCT cancer for the matched case patient. When possible, control patients were matched to case patients based on race (white, black, other) and on geographic region of the CIBMTR transplantation team (United States/Canada, Europe, Australia/New Zealand, Asia). Using the above criteria, we were able to match 1 control for 6 cases, 2 controls for 43 cases, 3 controls for 129 cases, 4 controls for 3 cases, and 5 controls for 2 cases. Primary analyses focused on 58 SCC case patients and the corresponding 155 matched control patients. Sites of the 58 SCCs were buccal cavity (n = 24), skin (nonmelanoma, n = 19), and other anatomic locations (n = 15) (Table 1). Secondary analyses evaluated 125 case patients with non-SCC cancers and their 346 matched controls. Sites of the 125 non-SCC solid tumors were skin (melanoma, n = 22), digestive tract (n = 19), brain (n = 18), thyroid (n = 15), female breast (n = 14), bone and connective tissue (n = 12), male and female genital tract (n = 10), respiratory system (n = 6), salivary glands (n = 4), and other anatomic locations (n = 6).

Data collection

CIBMTR and FHCRC transplantation data files were used to obtain information on demographic characteristics, transplantation procedures, and posttransplantation follow-up variables. The following additional information was extracted from the transplantation center medical records until the time of diagnosis of a solid cancer for case patients or the corresponding matched time interval for control patients using a standardized abstract form developed at the National Cancer Institute: GVHD prophylaxis (including T-cell depletion), dates and severity of acute GVHD, dates of chronic GVHD, severity of chronic GVHD (CIBMTR only), types of drugs used to treat GVHD (or other non-drug GVHD therapy), and duration of therapy for acute and chronic GVHD. Chronic GVHD case patients included patients with clinically extensive disease for FHCRC and those with any grade (mild, moderate, severe) of chronic GVHD for CIBMTR.[17] Additionally, data on pretransplantation chemotherapy (including specific drugs and duration of therapy), radiotherapy (including field and dose), smoking, and alcohol consumption (as determined at the time of transplantation) were abstracted from the medical records. The study was based on anonymized data and was classified as exempt by institutional review boards.

Information on duration of drug therapy for GVHD was available for 87.4% of the case patients and 89.8% of control patients. For 11.5% of case patients and 9.2% of control patients with known information on acute and chronic GVHD but with unknown start or end dates of GVHD therapy, we estimated the duration of immunosuppressive drug treatment using the median duration among control patients, stratified by occurrence of chronic GVHD, source of data, and type of drug. For 1.1% (n = 2) of case patients and 1.0% (n = 5) of control patients, it could not be determined whether chronic GVHD occurred or whether therapy was given; these patients were excluded from all analyses. Sensitivity analyses were conducted that included only those patients with excellent or good quality estimates of duration of immunosuppressive drug therapy, and the results were unchanged.

Statistical analysis

The primary focus of the current analysis was the association between GVHD and risk for SCC, based on our earlier cohort study that showed chronic GVHD to be a strong risk factor for subsequent SCC of the oral cavity and skin with no elevation in risk observed for non-SCCs.[10] We conducted parallel analyses of the association between GVHD and non-SCC tumors to confirm our earlier findings, and these results are presented briefly here.

Estimates of the relative risk for new malignancy associated with specific GVHD treatments were calculated by comparing the case patients' histories of exposure with those of their individually matched control patients within the matched time window of interest using multivariate conditional logistic regression methods.[18] Two-sided *P* values and 95% confidence intervals (CIs) were calculated.

The total duration of drug therapy for GVHD, including prophylaxis and therapy for acute and chronic GVHD, was determined by summing all nonoverlapping segments of all immunosuppressive therapy given within the relevant time interval. Total duration of chronic GVHD drug therapy was computed similarly. We also calculated separately the duration of exposure to cyclosporine (CSP) and to azathioprine (AZA) (Table 1). Corticosteroid therapy was typically given to patients whose therapy also included CSP or AZA; thus, its duration could not be separately evaluated. The major drugs used for prophylaxis and GVHD therapy—in addition to CSP, AZA, and steroids—included methotrexate, thalidomide, cyclophosphamide, and antithymocyte globulin (ATG). Psoralen and ultraviolet A light therapy (PUVA) to the skin or limited field irradiation was generally given in combination with multiagent CSA or AZA drug therapy (10 of 11 exposed patients).

For duration–response analyses, patients were categorized into evenly spaced groups of duration (months), with additional subgroups provided (when numbers permitted) for patients with 12 and 24 months or longer durations of therapy. Continuous variables were used for tests for trend over increasing duration of GVHD therapy. For analyses pertaining to individual drugs, patients were grouped into mutually exclusive categories.

Results

Patient characteristics

Characteristics of SCC case and matched control patients are given in Table 1. The predominant underlying primary diseases for patients in whom SCC developed were leukemia and severe aplastic anemia. Median age at HSCT was 26.5 years (range, 3.5-61.3 years), and the median time from HSCT to solid tumor diagnosis was 7.0 years (range, 0.9-22.9 years). Approximately 72% of all patients with SCC were male. Seventy-two percent of SCC patients and 52% of control patients had chronic GVHD.

Using data from our cohort, we calculated that the cumulative incidence of SCC was 1.1% at 20 years (95% CI = 0.7-1.7) in analyses adjusting for the competing risk for death.[19] Of the 58 patients with new SCCs, 27 died; in 18 of the deceased patients, SCC was the primary or secondary cause of death. The median survival time after a new invasive SCC of the oral cavity, skin, or other cancer site was 1.7, 4.1, and 2.0 years, respectively.

Effects of acute and chronic GVHD and duration of therapy

Multivariate models constructed to assess the relationship between SCC and GVHD (occurrence and therapy) are shown in Tables 2 and 3. Analyses that did not consider type of drug therapy or duration of treatment showed that the risk for SCC among transplant recipients in whom chronic GVHD developed was nearly 3-fold higher (relative risk [RR] = 2.79) than it was in patients with no acute and no chronic GVHD (Table 2, model 1). Risks associated with chronic GVHD were higher among those with previous acute GVHD than among those with no acute GVHD. No elevation in risk was observed for patients with acute GVHD but no chronic GVHD. Subsequent models found a strong association between the risk for SCC and the duration of immunosuppressive drug use, using patients with no or with less than 6 months of GVHD therapy as the reference group (Table 2, model 2). Although the test for trend of increasing risk with increasing duration was highly significant ($P < .001$), the pattern of risk was most consistent with a threshold effect, with risk increasing sharply to nearly 6-fold among patients treated for 24 months or more. In a model considering only drugs given to treat chronic GVHD, we found an 8-fold higher risk for SCC after 24 months or more of therapy (Table 2, model 3) compared with no chronic GVHD therapy. In models 2 and 3, after adjustment for the duration of immunosuppressive therapy, there was no independent association between occurrence of chronic GVHD and SCC risk (RR = 2.08; $P = .20$; data not shown). Therefore, chronic GVHD was not included in subsequent models. In parallel analyses of 128 transplant recipients in whom non-SCC solid tumors developed and their 346 matched control patients, we found no relationship between the development of chronic GVHD and the risk for non-SCCs (RR = 0.73; $P = .19$; data not shown). Similarly, there was no association between risk for non-SCC tumors and duration of chronic GVHD therapy (RR = 0.71, 0.83, and 0.77 for durations of 1-11, 12-23, and 24+ months, respectively; $P > .32$).

Type of immunosuppressive therapy and SCC

Additional models were constructed to assess whether the type of immunosuppressive drugs given to treat chronic GVHD was associated with the development of SCC (Table 3, model 1). Transplant recipients who received AZA, CSP, and steroids during the course of their chronic GVHD therapy had a highly significant 18-fold increased risk for SCC compared with those with no chronic GVHD therapy (Table 3, model 1). The risk was further heightened to more than 50-fold when other drugs, PUVA, or limited field irradiation were used in addition to AZA, CSP, and steroid therapy (11 cases, 3 controls; $P < .001$; data not shown). A borderline significant 3-fold increase in SCC risk was observed among patients given AZA and steroids without CSP, whereas no excess was found for those receiving CSP-based therapy (no AZA) or for recipients given steroids alone or other therapy (not including AZA or CSP).

Because type of immunosuppressive drug therapy for chronic GVHD was strongly correlated with duration of therapy, we further examined the duration–response relationship separately in mutually exclusive groups according to the drug regimens received compared with the reference group of patients not given chronic GVHD therapy (Table 3, models 2a-c). Risk for SCC increased with longer term duration therapy when the chronic GVHD therapy included AZA (Table 3, models 2a-b); 72% of patients given AZA, CSP, and steroids and 61% of those receiving AZA and steroids (no CSP) were treated for 24+ months. Especially high risks were found for prolonged durations of therapy (24+ months), which included AZA, CSP, and steroids (Table 3, model 2a). In contrast, only 6% of those given CSP-based therapies (no AZA) had similarly long durations (24+ months) of therapy, limiting our ability to estimate risk in this subgroup (Table 3, model 2c). However, we found no measurable elevation in SCC risk after CSP-based therapies given for 1 to 11 or 12 to 23 months.

The high risk for SCC that was associated with long-term chronic GVHD therapy, in particular with AZA therapy, may indicate that these variables were simply markers for severity of chronic GVHD. Because the database of the CIBMTR provided a severity grading of chronic GVHD, separate analyses regarding the effect of GVHD severity on the development of SCC were carried out based on 40 case patients and 102 control patients (Table 4, models 1-3). These data show that risk for SCC increased with increasing grade of chronic GVHD (*P* trend, $< .001$), with patients with severe disease having 10-fold greater risk than those without chronic GVHD (Table 4, model 1). Among transplant recipients with the most severe disease, all SCC case patients (13 of 13) and most control patients (4 of 6) received therapy including AZA (RR = 16.24; Table 4, model 2). Thus, we were unable to evaluate risk associated with CSP-based therapies among those with severe disease. However, among recipients with moderate grade chronic GVHD, we found an overall 6-fold elevated risk for SCC for those given AZA-based therapy, with no excess observed after therapy without AZA. Although numbers were sparse, there was evidence that risk increased with longer duration (12+ months) of AZA therapy within the moderate grade subgroup (RR = 14.96; $P = .007$; Table 4, model 3).

Specific tumor sites

Additional analyses assessed risk associated with duration of chronic GVHD therapy and type of immunosuppressive drugs for specific SCC sites. Chronic GVHD was most strongly associated with risk for invasive SCC of the skin, though the confidence interval was wide (RR = 14.46; Table 5, model 1). However, for SCC of both the skin and the buccal cavity, we observed significantly increased risks with more than 24 months of total GVHD therapy (Table 5, model 2). High risks were also seen for patients receiving long-term (24+ months) chronic GVHD drug therapy (Table 5, model 3). Chronic GVHD therapy including AZA was significantly associated with risk for each SCC cancer site but was strongest for SCC of the skin (RR = 20.84). Results were unchanged in analyses excluding the 3 case patients with buccal cancer (and their matched control patients) with Fanconi anemia, a condition known to be associated with a high risk for SCC and leukemia,[20] and in analyses adjusting for tobacco and alcohol consumption. Although numbers were sparse, there was also a suggestion that the risks for patients with SCC at other sites

Table 1. Characteristics of case patients with second squamous-cell carcinoma (SCC) and matched control patients

Characteristics	Case patients, no. (%)	Control patients, no. (%)
SCC location[a]		
Buccal cavity	24 (41.4)	—
Nonmelanoma skin, invasive	19 (32.8)	—
Male and female genitalia	9 (15.5)	—
Other	6 (10.3)	—
Registry[b]		
CIBMTR	40 (69.0)	102 (65.8)
FHCRC	18 (31.0)	53 (34.2)
Sex[b]		
Male	42 (72.4)	114 (73.6)
Race[b]		
White	52 (89.7)	141 (91.0)
Black	2 (3.4)	1 (0.7)
Other	4 (6.9)	13 (8.4)
Geographic region of transplantation center[b]		
United States/Canada	30 (51.7)	78 (50.3)
Europe	21 (36.2)	61 (39.4)
Other	7 (12.1)	16 (10.3)
Primary disease[b]		
Acute lymphoblastic leukemia	6 (10.3)	18 (11.6)
Acute non-lymphocytic leukemia[c]	15 (25.9)	35 (22.6)
Chronic myelogenous leukemia	14 (24.1)	40 (25.8)
Lymphoma, multiple myeloma	1 (1.7)	2 (1.3)
Severe aplastic anemia	17 (29.3)	47 (30.3)
Fanconi anemia	4 (6.9)	10 (6.5)
Hemoglobinopathies	1 (1.7)	3 (1.9)
Chemotherapy to treat primary disease		
Any chemotherapy		
No	12 (20.7)	31 (20.0)
Yes	44 (75.9)	123 (79.3)
Unknown	2 (3.4)	1 (0.7)
Alkylating agent therapy	11 (19.0)	33 (21.3)
Epipodophyllotoxins	5 (8.6)	11 (7.1)
Radiotherapy to treat the primary disease[d]		
No	52 (89.7)	140 (90.3)
Yes	5 (8.6)	12 (7.7)
Unknown	1 (1.7)	3 (1.9)
Age at transplantation[b]		
Younger than 10 y	6 (10.3)	16 (10.3)
10-19 y	13 (22.4)	40 (25.8)
20-29 y	13 (22.4)	29 (18.7)
30-39 y	13 (22.4)	35 (22.6)
40-49 y	9 (15.5)	24 (15.5)
50 y or older	4 (6.9)	11 (7.1)
Interval between first transplantation and SCC[b]		
Less than 1 y	4 (6.9)	10 (6.5)
1-4 y	15 (25.9)	42 (27.1)
5-9 y	26 (44.8)	67 (43.2)
10-14 y	9 (15.5)	25 (16.1)
15 y or more	4 (6.9)	11 (7.1)
Donor-recipient relationship		
HLA-identical sibling	54 (93.1)	142 (91.6)
HLA-1 antigen mismatched, matched family member	2 (3.5)	10 (6.5)
Unrelated donor	2 (3.5)	3 (1.9)
Transplantation conditioning regimens		
TBI + Cy ± other drugs	28 (48.3)	75 (48.4)
TBI ± other drugs, no Cy	1 (1.7)	8 (5.2)
TBI + LFI ± drugs	2 (3.5)	2 (1.3)
LFI ± drugs	7 (12.1)	13 (8.4)
Busulfan + Cy ± other drugs	9 (15.5)	16 (10.3)
Cy ± other drugs	11 (19.0)	39 (25.2)
Other	0 (0.0)	2 (1.3)
History of smoking and alcohol use at time of transplantation for SCC buccal cavity cases and controls[e]		
Current or past smoker	7 (29.2)	15 (22.4)
Never smoker	12 (50.0)	34 (50.8)

Table 1. Characteristics of case patients with second SCC and matched control patients (Continued)

Characteristics	Case patients, no. (%)	Control patients, no. (%)
History of smoking and alcohol use at time of transplantation[e]		
Unknown smoker	5 (20.8)	18 (26.9)
Alcohol use	5 (20.8)	19 (28.4)
No alcohol use	14 (58.3)	34 (50.8)
Unknown alcohol use	5 (20.8)	14 (20.9)
GVHD prophylaxis		
T-cell depletion of marrow[f]	6 (10.3)	9 (5.8)
GVHD prophylaxis, drugs[g]		
CSP ± other, no MTX	19 (32.8)	47 (30.3)
MTX ± other, no CSP	24 (41.4)	63 (40.7)
CSP + MTX ± other	12 (20.7)	43 (27.7)
Other,[h] unknown	3 (5.2)	2 (1.3)
Acute GVHD, severity		
None	21 (36.2)	57 (36.8)
Grade 1	11 (19.0)	44 (28.4)
Grades 2-4	26 (44.8)	53 (34.2)
Unknown	0 (0.0)	1 (0.6)
Acute GVHD therapy[g,i]	29 (100.0)	66 (100.0)
CSP ± other, no steroids	2 (6.9)	3 (4.6)
Steroids ± other, no CSP	21 (72.4)	48 (72.7)
CSP + steroids ± other	3 (10.3)	10 (15.2)
Other, unknown, no CSP, no steroids	3 (10.3)	5 (7.6)
Any ATG given for conditioning, prophylaxis, acute GVHD	8 (13.8)	20 (12.9)
Chronic GVHD		
No	16 (27.6)	74 (47.7)
Yes	42 (72.4)	80 (51.6)
Unknown	0 (0.0)	1 (0.7)
Therapy for chronic GVHD[g]	42 (100.0)	80 (100.0)
CSP	3 (7.1)	6 (7.5)
CSP, steroids	4 (9.5)	18 (22.5)
CSP, steroids, other[j]	0 (0.0)	4 (5.0)
CSP, AZA	0 (0.0)	1 (1.3)
CSP, AZA, steroids	7 (16.7)	5 (6.3)
CSP, AZA, steroids, other	9 (21.4)	3 (3.8)
AZA, steroids	7 (16.7)	12 (15.0)
AZA, steroids, other	2 (4.8)	2 (2.5)
Steroids	3 (7.1)	10 (12.5)
Steroids, other	1 (2.3)	5 (6.3)
Other[k]	0 (0.0)	2 (2.5)
Chronic GVHD therapy, unknown	1 (2.3)	2 (2.5)
Chronic GVHD therapy, none	5 (11.9)	10 (12.5)
Relapse, recurrence after transplantation[g]	1 (1.7)	17 (11.0)

Fifty-eight case patients and 155 control patients were included in the analysis. Percentages do not always add to 100% because of rounding.

TBI indicates total body irradiation; LFI, limited field irradiation; Cy, cyclophosphamide; CSP, cyclosporine; MTX, methotrexate; GVHD, graft-versus-host disease; ATG, antithymocyte/antilymphocyte globulin or serum; and AZA, azathioprine.

[a]Sites of buccal cavity SCC are lip (5), tongue (12), gum and other mouth (6), and hypopharynx (1). Sites of invasive skin SCC are face/jaw/cheek (3), lip (2), neck (2), shoulder (1), back (1), hand (1), leg (2), foot (2), unspecified (5). Sites for genital SCC include cervix (5 including 3 in situ), vulva (2 including 1 in situ), penis (2 including 1 in situ). Sites of other SCC include rectum (1), in situ anus (1), larynx/pharynx (1), lung (3 including 1 in situ).

[b]Control patients were matched to second cancer case patients on the following factors: registry (CIBMTR, FHCRC), type of transplantation (allogeneic, syngeneic), primary disease, sex, age at transplantation (within 3 years), interval between transplantation date and date of second cancer for the case patient (control patient had to survive at least as long as this interval, and collection of treatment data stopped at the end of the interval), race (United States case patients only), and geographic region of transplantation team (United States/Canada, Europe, Australia/New Zealand, Asia, other).

[c]Acute nonlymphocytic leukemia includes acute leukemia, unclassified.

[d]Radiotherapy to treat the primary disease includes radiation delivered to a field within or near the site of second SCC before the date of second cancer diagnosis or equivalent treatment cutoff date among control patients.

[e]Analysis based on 24 case patients with SCC of the buccal cavity and 67 matched controls.

[f]Category includes 1 patient with T cell depletion for second transplantation (2 case patients and 3 control patients who underwent second transplantation were included in the analysis).

[g]Categories include all GVHD occurrence/therapy/relapse during the matched time interval (interval between transplantation and second cancer diagnosis for the case patient or matched time interval for the control patient).

[h]Other includes T-cell depletion only, other, or no prophylactic drugs.

[i]In some transplantation centers, therapy for acute GVHD, which continued from GVHD prophylaxis, was listed on abstract forms under GVHD prophylaxis; therefore, prophylaxis therapy and treatment for acute GVHD were grouped for analysis.

[j]Other therapy for chronic GVHD included PUVA skin irradiation, limited field irradiation, and/or other less frequently used drugs (including cyclophosphamide, ATG, thalidomide, xomazyme, tacrolimus [FK506], procarbazine, 6 mercaptopurine [6-MP], interferon, pentaglobin, monoclonal antibodies, mycophenolate mofetil [MMF], methotrexate, and thymosin).

[k]Chronic GVHD therapy for patients with other therapy alone included methotrexate only (1 control patient) and 6-MP only (1 control patient).

Table 2. Risk for squamous-cell carcinoma (SCC) according to acute and chronic GVHD and duration of immunosuppressive therapy for GVHD

Risk factors	Case patients, no.	Control patients, no.	RR	95% CI	*P*
Model 1: acute, chronic GVHD*					
No acute, no chronic	11	52	1.00	Reference	—
Acute but no chronic	5	22	0.91	0.29-2.87	.87
Any chronic GVHD	42	80	2.79	1.28-6.06	.01
Chronic but no acute†	21	49	2.30	0.95-5.57	.07
Acute and chronic†	21	31	3.33	1.41-7.87	.006
Unknown acute or chronic	0	1	—	—	—
Model 2: total duration of immunosuppression prophylaxis, acute and chronic GVHD therapy, mo‡					
None, less than 6	15	51	1.00	Reference	—
6-11	6	37	0.58	0.17-1.89	.36
12-23	11	40	1.37	0.50-3.77	.54
24 or greater	26	25	5.60	2.07-15.19	<.001
24-47§	11	13	4.75	1.27-17.78	.02
48 or greater§	15	12	6.20	1.97-19.50	.002
Unknown	0	2	—	—	—
Model 3: duration of chronic GVHD therapy, mo‡‖					
None	21	84	1.00	Reference	—
1-11	6	26	1.00	0.35-2.85	.99
12-23	8	27	1.37	0.50-3.72	.54
24 or greater	23	16	8.44	3.17-22.47	<.001
24-47¶	10	6	22.57	2.63-193.6	.005
48 or greater¶	13	10	6.26	2.16-18.16	<.001
Unknown	0	2	—	—	—

There were 58 case patients and 155 control patients.

*Acute GVHD includes grades 2-4 acute GVHD.

†Includes the same variables as in the rest of model 1, with the variable *any chronic GVHD* separated into *chronic but no acute* and *acute and chronic* GVHD categories.

‡Total duration (model 2) and duration of chronic GVHD drug therapy (model 3) include months of therapy with immunosuppressive drugs.

§Model includes the same variables as in model 2, with duration *24 or greater* separated into *24-47* and *48 or greater.*

‖The reference group of model 3 includes 16 case patients and 74 control patients with no chronic GVHD and 5 case patients and 10 control patients who acquired chronic GVHD that did not require therapy.

¶Model includes the same variables as in model 3, with duration variables *24 or greater* separated into *24-47* and *48 or greater.*

(anogenital area; digestive and respiratory tracts) were increased after 24 months or more of chronic GVHD therapy compared with those with no chronic GVHD therapy (4 cases, 3 controls; RR = 4.61; P = .10; data not shown).

Other potential risk factors for SCC

In multivariate analyses that accounted for duration of chronic GVHD therapy, we found no significant association between SCC risk and risk factors related to the transplantation procedure, pretransplantation therapy for the primary disease, or posttransplantation recurrence or relapse (Table 6). Based on small numbers, we found a nonsignificant 3-fold risk for conditioning regimens including limited field irradiation, such as total lymphoid or thoraco-abdominal irradiation (RR = 3.0; P = .27), as previously reported.[9,10,21] In an evaluation of SCC of the buccal cavity, we found no evidence that risk was related to tobacco use (RR = 1.38; P = .66) or alcohol use (RR = 0.44; P = .30) when measured at the time of transplantation (data not shown).

Discussion

The present international case–control study is the largest analysis of HSCT patients to date to evaluate the role of GVHD and its treatment in the risk for solid cancers. We found that the strongest risk factors for SCC were long duration of immunosuppressive drug treatment for chronic GVHD, particularly with the use of AZA, and severity of chronic GVHD. Risks for SCC were especially high for patients receiving combined therapy that included AZA, CSP, and steroids. For SCCs of the skin and buccal cavity, we observed significantly increased risks with long-term GVHD therapy and use of AZA. Consistent with our previous cohort study,[10] we found no evidence that the occurrence of chronic GVHD or that GVHD therapy of long duration was related to the development of non-SCC solid cancers.

The major predisposing factor for chronic GVHD is preceding acute GVHD, a syndrome characterized by alloreactivity and immunodeficiency.[22] Immunodeficiency is further aggravated by the treatment of chronic GVHD, which may continue for several years. However, chronic GVHD, which most frequently affects the skin, liver, mouth, and eyes, also shows features of autoimmunity and inflammation. Both aspects are relevant because patients with autoimmune disorders are known to develop malignant tumors more frequently than persons with apparently normal immunity.[23] Chronic inflammation and scar formation have also been associated with an increased risk for cancer.[24,25] The interactions between inflammation and immunosuppression are not fully understood, but it may be speculated that immunosuppression from therapy administered in a milieu of inflammation, as occurs with chronic GVHD, would interfere with tissue repair, thereby enhancing the risk for tumor evolution. The risk would be further heightened with immunosuppressive therapies given for prolonged periods, as has also been seen in previous investigations of recipients of organ transplants.[16,26-29] If immunosuppressive therapy consisted of compounds such as AZA, known to be carcinogenic and to be implicated in the development of malignancies after

Table 3. Effect of type and duration of drug therapy for chronic GVHD on the risk for squamous-cell carcinoma (SCC)

Risk factors	Case patients, no.	Control patients, no.	RR	95% CI	*P*
Model 1: chronic GVHD therapy					
None	21	84	1.00	Reference	—
AZA, CSP, steroids, ± other therapy*	16	9	18.61	4.00-86.62	<.001
AZA, steroids, no CSP†	9	14	2.77	0.93-8.25	.07
CSP, no AZA, ± steroids‡	7	28	0.99	0.35-2.84	.99
Steroids/other drugs, no CSP, no AZA§	4	17	0.88	0.25-3.10	.84
Unknown AZA/CSP therapy	1	3	—	—	—
Model 2: duration of chronic GVHD therapy for specific drugs‖					
a: AZA, CSP, steroids, ± other therapy					
1-11 mo	2	3	5.43	0.63-46.60	.12
12 mo or more	14	6	38.71	4.69-319.5	<.001
12-23 mo	1	1	Infinite	—	—
14 mo or more	13	5	37.59	4.53-311.9	<.001
b: AZA, steroids, no CSP					
1-11 mo	1	8	0.67	0.08-6.02	.72
12 mo or more	8	6	5.05	1.37-18.65	.02
12-23 mo	5	4	4.99	1.00-24.97	.05
24 mo or more	3	2	5.14	0.80-33.13	.09
c: CSP, no AZA ± steroids					
1-11 mo	3	16	0.73	0.19-2.82	.64
12 mo or more	4	12	1.52	0.39-5.90	.54
12-23 mo	3	10	1.22	0.26-5.64	.80
24 mo or more	1	2	3.41	0.23-50.77	.37

Other drug therapy indicates chronic GVHD therapy other than CSP, AZA, or steroids. There were 58 case patients and 155 control patients.

*Eleven of the 16 case patients who had AZA-CSP-steroid therapy had other chronic GVHD drug therapy (mainly cyclophosphamide [4], thalidomide [3]). In addition, 4 case patients had PUVA skin irradiation and 2 case patients had limited field radiation for GVHD. Two of the 9 control patients with AZA-CSP-steroids had other chronic drug therapy (cyclophosphamide [1], thalidomide [2]), and 2 had PUVA skin irradiation. All but 1 patient (control) in the AZA-CSP-steroids group had steroids for chronic GVHD therapy.

†Two of the 9 case patients with AZA-steroids (no CSP) had other drug therapy; 2 of the 14 control patients had other drug therapy; none had PUVA skin irradiation or limited field radiation.

‡Four of the 7 case patients with CSP (no AZA) also had steroid therapy, and the remaining 3 case patients had CSP alone (none of the case patients had other drugs, PUVA skin irradiation, or limited field radiation therapy). Twenty-two of the 28 control patients with CSP (no AZA) also had steroid therapy, and the remaining 6 case patients had CSP alone. Three of the control patients with CSP (no AZA) had other drugs in addition to CSP and steroids, and 2 of the control patients had additional therapy with steroids and PUVA skin irradiation.

§Three of the 4 case patients in the steroids–other drugs (no CSP, no AZA) group received steroids alone, and the fourth case patient received another drug plus limited field irradiation; 14 of the 17 control patients in this therapy group received steroids, including 4 with steroids and other drugs; the other 3 control patients were treated with other drugs, no steroids.

‖Models 2a-c have as the reference group patients with no chronic GVHD therapy (21 case patients and 84 control patients). Models are also adjusted for the other drug groups (4 variables), as shown in model 1. Duration for model 2a is based on the combined duration of CSP and AZA, accounting for overlap in therapy, whereas the duration for model 2b is based on duration of AZA therapy and the duration for model 2c is based on duration of CSP therapy.

solid organ transplantation,[30] then one might expect to observe new malignancies in the HSCT setting. In fact, such an association was noted previously in patients who underwent transplantation for severe aplastic anemia,[3,9,31] though not all reports agree.[7] The present analysis strongly supports the initial findings in patients with aplastic anemia but also suggests that other components, in particular interactions with other agents, such as CSP, and the duration of treatment and the severity of chronic GVHD are contributing factors. Reports from the early 1980s suggested that CSP, in many instances given at doses much higher than in use today,[32] contributed to the development of malignancies, in particular, posttransplantation lymphoproliferative disorders.[33] More recent work suggests that CSP may induce phenotypic changes and may enhance invasiveness of nontransformed cells through a transforming growth factor-β (TGF-β)–dependent mechanism.[34]

The impact of CSP in combination with AZA, as observed in the present analysis, may conceivably be related to an enhancement of the mutagenic effect of AZA by the concurrent administration of CSP. On the other hand, most studies in renal transplant patients failed to show an increased rate of cancer development with a combination of AZA and CSP,[28] though the evidence is conflicting.[35] However, recipients of solid organ transplants, as a rule, do not experience GVHD, which generates its own processes of tissue destruction and repair and may render tumor development more likely in HSCT recipients.

Although the biologic mechanisms underlying the excess risk for posttransplantation SCC are still unclear, prolonged periods of immune suppression could result in the propagation of oncogenic viral infections and the suppression of antiviral immunity, leading to an excess of viral-related malignancies. Studies of recipients of organ transplants have associated human papillomavirus infection with SCCs of the anogenital region and skin,[16,36,37] and recent reports suggest that human papillomavirus infection may play an etiologic role in selected types of oral cavity cancers arising in immunocompetent populations.[38]

Because the increased risk associated with treatment may be a marker of severity of chronic GVHD, we attempted to address this issue in a subgroup of patients from the CIBMTR for whom data were known. In the subanalysis, we found a significant association between increasing grade of chronic GVHD and occurrence of SCC. Moreover, within the 2 subgroups of patients with moderate and severe chronic GVHD, the prolonged use of AZA remained the dominant risk factor for SCC. However, it was difficult to separate the duration and type of drug regimen used from the severity and refractoriness of chronic GVHD because patients with more severe

Table 4. Risk for squamous-cell carcinoma (SCC) associated with severity of chronic GVHD, duration of therapy, and use of specific drugs (CIBMTR data only)

Risk factors	Case patients, no.	Control patients, no.	RR	95% CI	*P*
Model 1: chronic GVHD grade					
No chronic GVHD	11	49	1.00	Reference	—
Mild	6	30	1.03	0.32-3.30	.96
Moderate	10	17	2.73	0.90-8.35	.08
Severe	13	6	9.93	2.79-35.29	< .001
Model 2: chronic GVHD grade, chronic drug therapy					
No chronic GVHD, mild grade	17	77	1.00	Reference	—
Moderate, AZA	8	6	6.32	1.71-23.32	.006
Moderate, other drugs, no AZA	1	11	0.28	0.03-2.40	.24
Severe, AZA	13	4	16.24	4.04-65.34	< .001
Severe, other drugs, no AZA	0	2	0.00	—	—
Unknown drug therapy*	1	2	—	—	—
Model 3: chronic GVHD grade and duration of AZA therapy, mo†					
Moderate, AZA, 1-11 mo	2	4	2.26	0.34-15.21	.40
Moderate, AZA, 12 mo or more	6	2	14.96	2.08-107.5	.007
Severe, AZA, 1-11 mo	1	1	3.13	0.18-54.08	.43
Severe, AZA, 12-23 mo	4	1	16.75	1.41-199.0	.03
Severe, AZA, 24 mo or more	8	2	28.84	3.06-272.0	.003

Forty case patients and 102 control patients were included in these analyses.

*One case patient and 2 control patients with unknown types of drugs for chronic GVHD were excluded from the analysis.

†Model 3 reference group consisted of patients with *no chronic GVHD or mild grade chronic GVHD* (see model 2). Model 3 also accounts for other drug groups and includes variables for *moderate, other drugs (no AZA); severe, other drugs (no AZA);* and *unknown drug therapy.*

GVHD were more likely to receive therapy with AZA, CSP, and steroids over long periods of time.

An important strength of our study is the evaluation of a large international cohort of more than 24 000 transplant recipients, which allowed us to quantify cancer risks over a wide range of GVHD drug regimens and treatment patterns. In interpreting these findings, however, it is important to recognize that treatments for refractory chronic GVHD have shifted in the past 3 decades, with current patterns showing a preference for newer drugs such as tacrolimus (FK506) and mycophenolate mofetil (MMF) in addition to CSP and steroids. AZA is used infrequently in the current therapy for chronic GVHD at most transplantation centers, and its effectiveness for standard-risk chronic GVHD has been questioned in a randomized controlled trial from Seattle.[39] Although bone marrow was the source of stem cells in our study, peripheral blood stem-cell transplantation (PBSCT) is widely used in current treatments. Recent studies indicate that chronic GVHD may be more intense and more frequent in general after PBSCT,[40,41] which may alter the risk for subsequent SCC. We also acknowledge the limited data available from medical records on lifestyle factors. Although we

Table 5. Risk for squamous-cell carcinoma (SCC) of the buccal cavity and skin, according to chronic GVHD and duration of therapy

	SCC buccal cavity				SCC skin			
Risk factors	Case patients, no.	Control patients, no.	RR*	95% CI	Case patients, no.	Control patients, no.	RR	95% CI
Model 1: chronic GVHD								
No	5	24	1.00	Reference	3	29	1.00	Reference
Yes	19	42	2.35	0.70-7.93	16	22	14.46	1.84-113.3
Unknown	0	1	—	—	—	—	—	—
Model 2: total duration of prophylaxis, acute and chronic GVHD therapy								
None, less than 12 mo	7	34	1.00	Reference	7	32	1.00	Reference
12-23 mo	4	18	1.14	0.28-4.67	3	12	2.00	0.38-10.36
24 mo or more	13	14	5.65	1.53-20.79	9	7	12.00	2.02-71.38
Unknown	0	1	—	—	—	—	—	—
Model 3: duration of chronic GVHD therapy								
None, less than 12 mo	9	40	1.00	Reference	8	41	1.00	Reference
12-23 mo	4	17	0.99	0.25-3.93	3	6	2.32	0.42-12.91
24 mo or more	11	9	6.76	1.71-26.69	8	4	20.30	2.41-171.0
Unknown	0	1	—	—	—	—	—	—
Model 4: chronic GVHD drug therapy								
None, other, no CSP, no AZA	9	41	1.00	Reference	7	38	1.00	Reference
CSP, no AZA	3	13	0.78	0.17-3.51	2	8	1.23	0.13-11.78
Any AZA	11	11	5.47	1.41-21.16	10	5	20.84	2.57-169.1
Unknown CSP/AZA	1	2	—	—	—	—	—	—

For SCC buccal cavity, there were 24 case patients and 67 control patients; for SCC skin, there were 19 case patients and 51 control patients.

*Adjustment for smoking/alcohol consumption (at time of transplantation) in the buccal cavity model led to similar risk estimates.

Table 6. Risk for squamous-cell carcinoma (SCC) associated with risk factors other than GVHD in multivariate analyses adjusted for duration of chronic GVHD therapy

Risk factors	Case patients, no.	Control patients, no.	RR	95% CI	*P*
Transplantation-related factors					
Any TBI in conditioning regimen					
No	28	70	1.00	Reference	—
Yes	30	85	0.40	0.13-1.24	.11
High-dose TBI conditioning regimen, 13 Gy or higher					
No	35	98	1.00	Reference	—
Yes	23	57	0.99	0.44-2.22	.98
Any limited field radiation (TLI, TAI) as part of the conditioning regimen					
No	49	140	1.00	Reference	—
Yes	9	15	3.07	0.37-37.63	.27
T-cell depletion of donor bone marrow					
No	52	146	1.00	Reference	—
Yes	6	9	1.76	0.52-5.95	.36
Use of ATG in conditioning regimen or as GVHD prophylaxis or therapy					
No	50	135	1.00	Reference	—
Yes	8	20	1.02	0.39-2.65	.97
Donor-recipient relationship					
HLA identical sibling	54	142	1.00	Reference	—
HLA mismatched donor	2	10	0.82	0.17-4.05	.81
Unrelated donor	2	3	1.18	0.09-15.83	.90
Treatment of primary disease before transplantation					
Pretransplantation RT					
None, RT to distant site	52	140	1.00	Reference	—
Yes, RT within or near second cancer site	5	12	6.98	0.38-128.7	.19
Unknown RT	1	3	—	—	—
Duration of pretransplantation chemotherapy, mo					
None	12	31	1.00	Reference	—
1-11	29	83	0.49	0.13-1.86	.30
12 or greater	12	33	0.66	0.14-3.08	.59
Unknown chemotherapy or duration	5	8	—	—	—
Duration of pretransplantation alkylating agent therapy, mo					
None	45	119	1.00	Reference	—
1-5	5	14	0.78	0.19-3.14	.73
6 or greater	6	17	1.28	0.37-4.43	.70
Unknown duration	2	5	—	—	—
Pretransplantation chemotherapy, including epipodophyllotoxins					
No	51	141	1.00	Reference	—
Yes	5	11	1.10	0.31-3.94	.88
Unknown	2	3	—	—	—
Follow-up after transplantation					
Disease relapse or recurrence					
No	57	138	1.00	Reference	
Yes	1	17	0.16	0.18-1.39	.09

Analyses were based on 58 case patients and 155 control patients.

TBI indicates total body irradiation; TLI, total lymphoid irradiation; TAI, thoraco-abdominal irradiation; ATG, antithymocyte/antilymphocyte globulin or serum; RT, radiation therapy.

found no association between SCC of the buccal cavity and history of tobacco and alcohol exposure before transplantation, exposure to these carcinogens in the posttransplantation years might have influenced risk among these immunodeficient patients. However, the generally young age of HSCT recipients suggests that their cumulative exposure to tobacco and alcohol over the period of study was unlikely to be an important confounding factor. Previous studies in immunosuppressed recipients of organ transplants show strong correlations between risk for SCC of the skin and ultraviolet radiation,[16] but data were unavailable to address this question in our investigation.

In summary, this case–control study indicates that prolonged use of immunosuppressive drugs to treat chronic GVHD, particularly AZA, and severity of chronic GVHD are major risk factors for the development of SCC after HSCT. However, most patients in our study with severe, durable chronic GVHD were also treated with AZA, confounding our ability to attribute risk independently to either chronic GVHD or AZA therapy. Although characterization of the carcinogenic mechanisms requires further study, these data suggest an important immunologic component related to chronic GVHD, which increases with more intensive regimens and with duration of therapy. The differences in GVHD-related risk patterns between SCC and non-SCC are consistent with the hypothesis that different pathways are involved in the evolution of different solid tumors. These results provide further encouragement to strategies to prevent moderate to severe chronic GVHD and to the development of more effective and less carcinogenic regimens for treatment. Although the absolute risk for SCC in this cohort was low, we recommend that patients exposed to persistent chronic GVHD, prolonged immunosuppressive therapy, or both, undergo long-term surveillance so that these tumors may be detected at an early and potentially curable stage.

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Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study

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